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Published in:
Neuroscience and Biobehavioral Reviews

DOI:
[10.1016/j.neubiorev.2015.09.016](https://doi.org/10.1016/j.neubiorev.2015.09.016)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2015

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Looijestijn, J., Blom, J. D., Aleman, A., Hoek, H. W., & Goekoop, R. (2015). An integrated network model of psychotic symptoms. *Neuroscience and Biobehavioral Reviews*, 59, 238-250.
<https://doi.org/10.1016/j.neubiorev.2015.09.016>

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Review

An integrated network model of psychotic symptoms



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ARTICLE INFO

Article history:

Received 26 February 2015

Accepted 27 September 2015

Available online 30 September 2015

Keywords:

Psychosis

Schizophrenia

Hallucinations

Delusions

Network science

Integrative science

Attractor network

Neural networks

GABA inhibition

NMDA excitation

Neuromodulation

Dopamine

Default-mode network

Functional neuroimaging

Functional connectivity

Resting-state connectivity

Central executive network

Saliency network

Social networks

Scale free

ABSTRACT

The full body of research on the nature of psychosis and its determinants indicates that a considerable number of factors are relevant to the development of hallucinations, delusions, and other positive symptoms, ranging from neurodevelopmental parameters and altered connectivity of brain regions to impaired cognitive functioning and social factors. We aimed to integrate these factors in a single mathematical model based on network theory. At the microscopic level this model explains positive symptoms of psychosis in terms of experiential equivalents of robust, high-frequency attractor states of neural networks. At the mesoscopic level it explains them in relation to global brain states, and at the macroscopic level in relation to social-network structures and dynamics. Due to the scale-free nature of biological networks, all three levels are governed by the same general laws, thereby allowing for an integrated model of biological, psychological, and social phenomena involved in the mediation of positive symptoms of psychosis. This integrated network model of psychotic symptoms (INMOPS) is described together with various possibilities for application in clinical practice.

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1. Introduction

Worldwide schizophrenia is considered the most disabling of mental health conditions (Salomon et al., 2012), even though its etiology, epidemiology, and nosological status are subject of ongoing debate (Van Os et al., 2010; Blom and Van Praag, 2011; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Hogerzeil et al., 2014). For over a century the schizophrenia concept has provided a conceptual framework for clusters of psychotic symptoms that tend to have a protracted duration, but defy attribution to any known somatic condition. Bleuler (1908), who introduced the term, envisaged schizophrenia as a group of disorders rather than a single nosological entity. Nevertheless, during the past century numerous attempts have been made to link this variegated group of neuropsychological symptoms to a single etiological or pathophysiological process that may serve as a common pathway and, thus, confirm schizophrenia's status as a single-disease concept. As a corollary, schizophrenia has been attributed to several biological, psychological and interpersonal mechanisms, including psychophysical degeneration (Kraepelin, 1893), metabolic disorder (Kraepelin, 1896), a hypothetical neurotoxin called *Toxin X* (Jung, 1907), weakness of association (Bleuler, 1911), acute infectious disease (Menninger, 1927), deficiencies in glucose metabolism (Sakel, 1935), double binds in social interactions (Bateson et al., 1956), victimization by the nuclear family and/or society at large (Laing, 1959), abnormal methylation of catecholamines (Bourdillon et al., 1965), dopaminergic dysfunction (Snyder et al., 1974), genetic vulnerability (Kety et al., 1976), synaptic slippage (Meehl, 1990), atypical language lateralization (Crow, 1990), prefrontal–parietal lobe functional disconnection (Friston and Frith, 1995), membrane lipid disorder (Horrobin, 1996), and disturbances in salience regulation (Van Os, 2009). However, as none of these mechanisms applies to the whole group of individuals diagnosed with schizophrenia, and many additional risk factors (including prenatal stress, maternal famine during pregnancy, cannabis use, urbanization, and social defeat) have been identified, it is now customary to conceptualize schizophrenia in terms of a neuropsychiatric disorder with multiple etiologies, multiple clinical expressions, and an (often) unfavorable outcome. Andreasen (1999) summarized this general concept in her Unitary Model of Schizophrenia, and emphasized that the notion of unitarianism hinges on the presumed lathomenology – or common pathway – which connects those multiple etiologies and multiple clinical expressions.

The repeated failure to find empirical evidence for the existence of such a common pathway has led to increasing doubt about the usefulness of maintaining schizophrenia as a unitary nosological construct [for an overview of the various positions in this debate see Blom (2004) and Blom and Van Praag (2011)]. This has prompted a number of alternative approaches, ranging from pleas to abandon the concept altogether (Szasz, 1961; Van Praag, 1976; Bentall, 1992)

to attempts at reconceptualization with the aid of different types of classification (Leonhard, 1999; Van Os et al., 2000; First, 2006), endophenotypes (Cloninger, 1999; Lenzenweger, 1999; Braff et al., 2007) or more modest clusters of symptoms (Susser et al., 1996; Blom and Van Praag, 2011). While the concept's dissection with the aid of intermediate phenotypes is considered promising (Jablensky, 2011), and a proposal to link genomics to certain neural circuits may be viable in the near future (Cuthbert and Insel, 2010), the conceptualization of psychotic symptoms and their interconnectedness has remained an elusive task.

1.1. Aim

Drawing on insights from network science, the present paper seeks to approach the symptoms considered characteristic of schizophrenia in a different way, i.e. by addressing different levels of biological organization through a unifying framework. Recent breakthroughs in network science allow for a mathematical representation of an unprecedented number of interacting factors in a single model (Goekoop and Looijestijn, 2012). We apply those insights to a substantial number of clinical, neuroscientific, and sociological findings pertaining to the origin and expression of psychotic symptoms. Rather than attempting to solve the 'schizophrenia problem' by seeking to establish its alleged lathomenology, our goal is to define a single mathematical framework and corresponding language with which to describe the large number of (neuro)biological and social factors that contribute to the occurrence of psychotic symptoms as the result of interactions between events that take place at multiple spatial scale levels of organization. The end result will be an Integrated Network Model of Psychotic Symptoms (INMOPS), which can be examined for its ability to explain and predict events that contribute to the occurrence of psychotic symptoms (Fig. 1).

2. Network science

In mathematics, a network is a set of interconnected agents that can be identified separately in space. Within networks, agents can transfer their properties to other agents within and across different spatial scale levels of organization. Agents may be genes, for example, or proteins, which activate each other through chemical reactions; they may be neurons that fire and transfer their active state onto other neurons; they may be individual people in a social network who share ideas or emotions; or they may be companies that exchange cash flows in a global market (Girvan and Newman, 2002). In each case the agents and their interactions are modeled as network structures in which nodes are mutually connected through links that have a certain strength or weight (as expressed, for example, in terms of contact frequency). Throughout the 20th century, mathematicians assumed that all networks

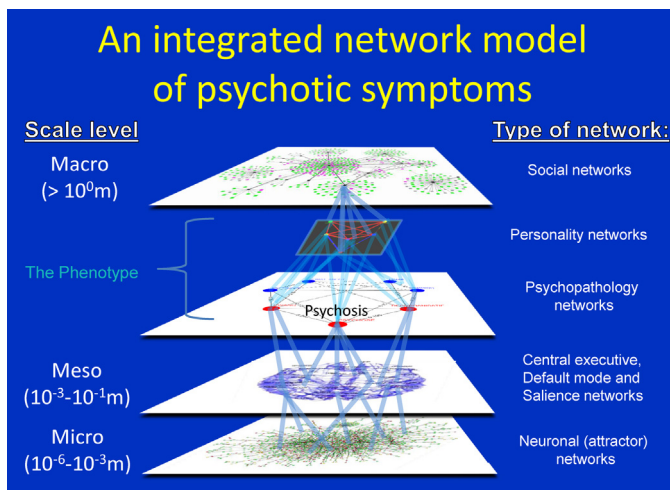


Fig. 1. An integrated network model of psychotic symptoms. The dynamic interplay between multiple scale levels of organization and their relationship to phenotypic experience is indicated by cross-connections within and between the various levels. Each level is governed by similar mathematical rules, as defined by the multimodal, hierarchic, and scale-free organization of the network as a whole. This allows for the study of psychotic symptoms in different fields of science using a single methodology and a common (mathematical) language.

consisted of agents that were randomly connected to each other and (on average) had the same number of links. That assumption was challenged when Watts and Strogatz (1998) discovered that most nodes in biological networks are not randomly connected but that most of them have few connections, while the remaining few have many (i.e., some 20% of all nodes 'own' some 80% of all links). The few richly connected nodes within networks are called *hubs*. Hubs can be compared to the center of a spider's web from whence direct access is possible to many other parts of the network. Because of the existence of hubs, each node within a network is only a small number of steps away from any other node, even when their physical distance can vary considerably. In social networks, for example, the average number of degrees of separation between all 'nodes' (people) is 5.9 ('everyone is only six handshakes away'). This plain number explains why it is not uncommon for us to meet a stranger in some distant country who turns out to be the best friend of our best friend's wife. Networks with this general topology are called *small-world* networks, after this peculiar phenomenon. The major hubs that connect large groups of people tend to be public figures such as school teachers, CEOs, politicians, and community center volunteers. Hubs surround themselves with large numbers of nodes and create numerous connections within their network. In this way they promote the formation of 'network communities', which are collections of nodes that are significantly better connected with each other than with all other nodes in the network (Girvan and Newman, 2002). Network communities can themselves be viewed as yet another set of nodes in a different network at a higher spatial scale level of organization. Thus networks may have 'superclusters' that represent 'communities of communities' which act as nodes at an even higher scale level of observation, and so on. Small-world network structures are found at all levels of biological organization, varying from molecules to cells, and from neural networks to social networks. Hence, similar network structures and corresponding mathematical rules can be found in *small-world* networks, regardless of the scale level of observation; this is why such structures are called 'scale-free' (or fractal-like) network structures (Barabási, 2009). Human beings consist of large collections of molecules, organelles, cells (neurons), tissues, and organs. Therefore, they can be conceptualized as giant, *scale-free* network structures (Barabási, 2009). Each spatial scale level has nodes or modules that are dedicated to the sensing of incoming information (e.g. receptors,

dendrites, sensory neurons, sensory cortices), the evaluation of this information (second-messenger pathways and genes, soma of the neuron, interneurons, brain areas involved in emotional and cognitive (salience) processing), and response formation (e.g. lysosomes, the axon, motor neurons, motor cortex). Each spatial scale level is characterized by its own unique spatial dimensions (e.g. micrometers to centimeters, centimeters to decimeters, etc.) and temporal dimensions (e.g. faster or slower oscillations of activity, etc.). Thus, network science offers a common mathematical framework and language that allows us to explore human (patho)physiology at different scale levels of organization. Below, we approach the positive symptoms of psychosis from the vantage point of this general framework.

3. Network science and psychosis

To date, one of the most common ways to identify groups of agents that somehow belong together in a collective is principal-component analysis (PCA). In medicine, PCA allows for the detection of groups of symptoms that have a tendency to co-occur within individuals (called 'principal components'). PCA studies have shown that 'schizophrenia' consists of multiple components of psychopathological symptoms (Van der Gaag et al., 2006). These components include 'positive symptoms' (such as hallucinations and delusions), 'negative symptoms' (such as retardation and psychomotor inhibition), and 'disorganization' (of speech, cognition, and behavior). In most individuals diagnosed with schizophrenia, these three basic components (or 'syndromes') come to expression to some significant degree. Moreover, they tend to go hand in hand with other symptom clusters, such as affective symptoms (depression, anxiety, anger), neurotic symptoms (obsessive-compulsive symptoms, phobias), cognitive symptoms (memory loss, mental retardation) or motivational symptoms such as mania (Goekoop and Goekoop, 2014).

Network community detection (a clustering technique based on network analysis) became available about 15 years ago. Similar to PCA, this technique allows to identify groups of symptoms (or network communities) that have a tendency to co-occur within and between patients. In psychiatry, such network communities show a large correspondence (i.e. >90%) with the principal components of psychopathology as established with the aid of PCA (Goekoop and Goekoop, 2014). However, unlike PCA, network community detection offers an explanation of *why* those symptoms tend to cluster together: not by proposing an external latent variable (e.g. an etiological or pathophysiological mechanism that may serve as its long-sought-after lathomenology), but by granting individual symptoms the status of causal agents that facilitate the occurrence of other symptoms (Borsboom and Cramer, 2013). As these causal agents have a tendency to create closed causal loops, all symptoms within a particular causal loop contribute to each other's existence. For example, increased tension levels may contribute to sleeping difficulties, which may induce fatigue, which may lead to concentration difficulties, which may lead to a proneness to errors, which may lead to actual errors, which may lead to a further increase of the tension level, etcetera. This general model of the *self-organization of mental disorders* is now rapidly gaining field, since it provides an explanation for the preferential connections between groups of symptoms in terms of the emergence of 'vicious circles' (or circularly causal relations) among individual symptoms (Borsboom et al., 2011). As shown in our 2014 paper, a network graph of interacting symptoms of psychopathology contains clusters of densely interacting symptoms that can be readily identified as 'elementary syndromes', such as Psychosis, Retardation and Disorganization. Such basic syndromes consist of vicious circles of individual symptoms of psychopathology. Interestingly, mental disorders at large (such as 'schizophrenia') can be conceptualized

as vicious circles between such elementary syndromes. Regarding the elementary syndrome that we call ‘psychosis’ (a combination of hallucinations and delusions), this syndrome can be seen as a vicious circle in which hallucinations trigger delusional explanations which, in turn, may strengthen hallucination proneness, etcetera. Causal relationships within this syndrome may be bidirectional and involve multiple different pathways, characteristic of the elementary syndrome of psychosis.

In this paper we restrict ourselves to a review of the positive symptoms of psychosis (i.e., the elementary syndrome of ‘psychosis’) since these constitute the core features of all psychotic disorders. As is shown, positive symptoms and their relationships involve changes in network structure and function across many different spatial and temporal scale levels of organization within the human brain. Current estimates indicate that the human brain has at least 20 different scale levels of neural organization (‘from molecules to mind’) (Sporns, 2012). As appropriate tools to cover all these scale levels and their mutual interactions have not yet been developed, we limit our discussion of neural correlates to two global levels of organization, which we designate as the micro- and mesoscale levels of organization. Finally, we demonstrate that the principals and mathematical laws that govern events at the neural micro- and mesoscale levels of organization also govern the social level of organization, i.e., the macroscale level of organization.

4. Network models of psychosis: scale levels of organization

At the microscale level, events are described at a spatial scale level of 10^{-6} to 10^{-3} m, which is the level where individual neurons combine into neuronal networks of micrometers to millimeters in diameter. At this scale level, the main task of networks is to represent the (combined) states of networks further ‘upstream’ in the general flow of information, to separate signal from noise, and to pass on activity to networks located further ‘downstream’ of the information flow (Freeman, 1999). Thus, a stimulus-evaluation-response network organization can be discerned already at the microscale level of organization. Within these networks, neuronal activity is a result of neurochemical changes (i.e., changes in neurotransmitter signaling pathways), changes in synaptic density and function, and (environmentally-induced) genetic expression profiles (The Network and Pathway Analysis Subgroup of the Psychiatric Genomics Consortium, 2015). This scale level is difficult to study using in vivo techniques, whereas in vitro techniques have the disadvantage of placing the important actors (network nodes) out of their natural context. To overcome these obstacles, findings from in vivo and in vitro studies can be combined in in silico models of neuronal interaction, e.g. in computer simulations. Based on the principles of computational neuroscience, such simulations help to understand how firing patterns of neuronal populations change when, for example, different receptor types are selectively stimulated or inhibited.

Below, we discuss the ability of such in silico models to cover the correlates of positive symptoms of psychosis at the microscale level of organization.

The mesoscale level of organization has a spatial scale level of 10^{-3} to 10^{-1} m, i.e., a distance of millimeters to decimeters. The main task of these networks is to represent the *milieu externe* of the organism in sensory cortices, to integrate information from all sensory modalities and information with an emotional or cognitive content, to evaluate these data streams in terms of salience, to develop motivational drive, to facilitate response selection (executive functioning), to execute premotor planning, and to generate motor output. Thus, a stimulus-evaluation-response loop can again be observed at the mesoscale level of organization. Network activity at this level is the net result of events taking place at all lower levels

of neurobiological organization. The mesoscale level can be studied in vivo using structural and functional magnetic resonance imaging (MRI and fMRI), electroencephalography (EEG), and magnetoencephalography (MEG). Since MRI has a spatial resolution superior to that of EEG and MEG we focus mainly on MRI findings (although EEG and MEG findings are also briefly mentioned).

Finally, we briefly address the social environment as the macroscale level of organization, since studies on the composition of social networks show that this level is also relevant for the development of positive symptoms of psychosis (Veling et al., 2014). Like neural networks, network communities in social networks develop through a process of self-reinforcement and suppression of neighboring communities. Information pertaining to the external world is shared among individuals, evaluated, and acted upon in a way that is similar to the way information is processed at the network’s lower levels of organization. We demonstrate that such processes may contribute to psychotic symptoms in their own idiosyncratic ways.

5. Network models of psychosis: the microscale level

Currently, one of the most sophisticated network models of the neurobiological correlates of psychotic symptoms at the microscale level stems from Loh et al. (2007). Their work starts from the central premise that the neural correlates of percepts can be described in terms of firing patterns of individual neurons within perception networks, and that those firing patterns display certain specific frequencies and amplitudes. Taking visual perception as an example, light reflected from an object in the extracorporeal world (say, a tree) activates retinal cells which, after a cascade of intermediary processes, recruit a particular subset of neurons in primary visual cortex that respond selectively to the various subcomponents of this stimulus (e.g. texture, color, movement). In conformity with the adage ‘neurons that fire together, wire together’, repeated exposure to similar objects leads to a strengthening of the synaptic connections between the cells of this ensemble through long-term potentiation (LTP) (Lomø, 2003). Thus, preferential connections are created between the neurons within this particular subset of neurons in visual cortex, yielding what we might call – in this case – a ‘tree network’. Such higher-order representations (leaves, branches, bark, etc.) are formed in secondary visual cortex. When there is no tree present in the percipient’s visual field, the tree network is at rest because it receives no dendritic input. When there are only leaves to be perceived, parts of the tree network may become activated (i.e., those involved in the coding for leaves), but the remainder of the network will remain at rest and no tree will be perceived. Only when the dendritic input reaches a critical threshold (i.e. when the input picture comprises essential parts such as bark, branches, and leaves), will the network be triggered in such a way that it mediates the perception of a tree. Incidentally, not all parts of the tree need to be present in the visual field in order for the tree network to respond in its entirety. When the input picture consists of a sufficiently large number of tree-like elements, the remainder of the tree network is activated as a form of ‘pattern completion’, which facilitates the perception of a tree. As soon as this particular network is activated by dendritic input, it passes its activity on to higher-order processing networks further downstream of the flow of information processing. Meanwhile, excitatory connections that emanate from the neurons of the tree network loop back to themselves and engage in auto-excitation (Fig. 2). Such positive feedback loops help to maintain an active state within the tree network, thus allowing for the creation of a stable percept and facilitating its storage in memory. In addition, the tree network stimulates inhibitory interneurons that connect to neighboring neurons not implicated in the tree network, thus

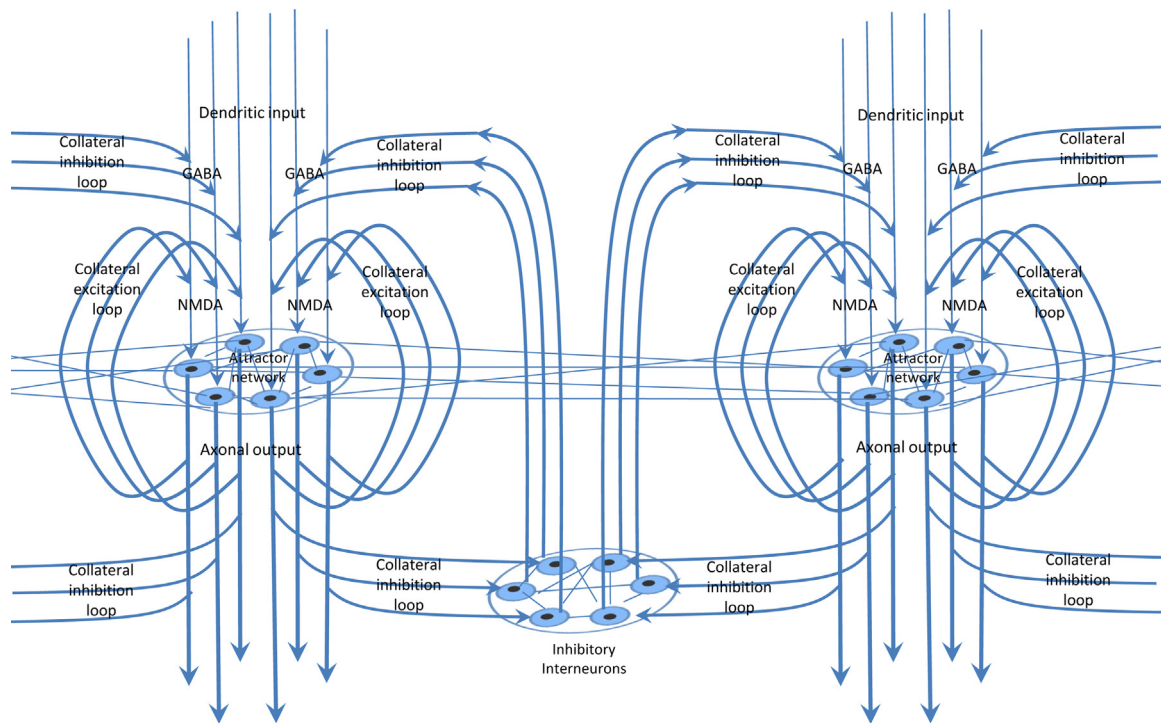


Fig. 2. Network structure of an attractor network. Two attractor networks are shown that are interconnected into a larger network. Dendritic input selects a subpopulation of neurons that constitute the attractor network for that particular stimulus. Excitatory (NMDA-related) output loops back onto the dendritic input connections, thus causing a self-perpetuation of attractor activity. Excitatory output also connects to (GABA-ergic) interneurons, which loop back to the dendritic input connections of all surrounding neurons whose activity is subsequently inhibited. Thus, attractor networks compete for activity by promoting the persistence of their own attractor states and suppressing activity in neighboring attractor networks. This is Nature's way of selecting those attractor states for which there is most 'empirical support'. Neuromodulatory neurotransmitters can shift the balance between noise suppression and auto-excitation (change signal-to-noise ratios), thereby allowing biases in the perception of particular stimuli. Dopamine 2 antagonists enhance collateral inhibition (noise reduction) by enhancing GABA-ergic neurotransmission, whereas Dopamine 1 agonists enhance auto-excitation by facilitating NMDA-receptor-mediated neurotransmission, thereby increasing the robustness of the attractor state (or signal). This network model is so generic that it can be used to describe attractor states at multiple levels of biological organization (i.e. the micro, meso and macrolevels described in this paper).

helping to suppress any percepts for which there is insufficient support in the perceptual input picture (i.e., 'noise'). Thus, neighboring perceptual networks are in a constant state of competition to represent external signals (Fig. 2).

5.1. Attractor networks and energy landscapes

In network science, networks that encode for particular percepts – such as the tree network – are known as *attractor networks* (Loh et al., 2007). Attractor networks are networks characterized by a more or less pronounced *attractor state*, which is a preferential (low energy) state toward which the network tends to converge by default. Regardless of its initial state, the network will eventually settle for that particular state. The attractor state is a function of the strength of the network's own synaptic connections, formed during prior episodes of learning (synaptic rewiring). In other words, the attractor state represents the information that has been stored in the network (e.g. a percept). Depending on the amount of energy that is applied to the network (e.g. intrinsic noise levels or dendritic stimulation), all brain networks have lower- and higher-energy attractor states. The effect of this can be further clarified by picturing a ping pong ball which has been moved uphill by applying energy to it (Fig. 3). When enough energy is applied to push it to the top, it can settle for a higher-energy stable (attractor) state. When insufficient energy is applied, the ping pong ball has no other option than to settle down in the valley at the foot of the hill and assume a lower-energy stable (attractor) state. The tiny amount of energy needed for the network to assume this low-energy 'resting state' is provided by random depolarizations within the network itself (i.e., internal noise) and sustained by the absence of any external

signals. Such low-energy resting states are characterized by low-frequency firing patterns that display a certain lability due to the fact that there is only little auto-excitation (Fig. 2). In perceptual networks, that activity may induce weak, fleeting percepts such as those characteristic of daydreaming, hypnagogia or actual dreaming. When more energy is applied in the form of dendritic input, networks will shift from their labile, low-energy attractor states to robust, high-energy attractor states with high-frequency firing patterns and the subsequent formation of robust percepts (Loh et al., 2007).

5.2. Psychosis at the microscale level of organization

5.2.1. Healthy individuals

In the idiom of network science, positive symptoms of psychosis are conceptualized as the experiential equivalents of robust, high-frequency attractor states that occur in the absence of adequate dendritic input. In other words, positive symptoms arise when perceptual or cognitive networks enter their high-energy attractor state when all they should do is remain in their low-energy attractor state. Several mechanisms have been proposed for this switching from true-negative (low-energy) to false-positive (high-energy) attractor states (Rolls and Deco, 2011). To illustrate these mechanisms, Fig. 3 provides a schematic illustration of network activity in an *energy landscape*. In this scheme, attractor states are represented as valleys or *attractor basins* in the landscape. When the differences in energy between the resting and active state are less pronounced, i.e., when the attractor basins are *shallow*, the transition from a low-energy resting state to a high-energy active state is achieved more easily.

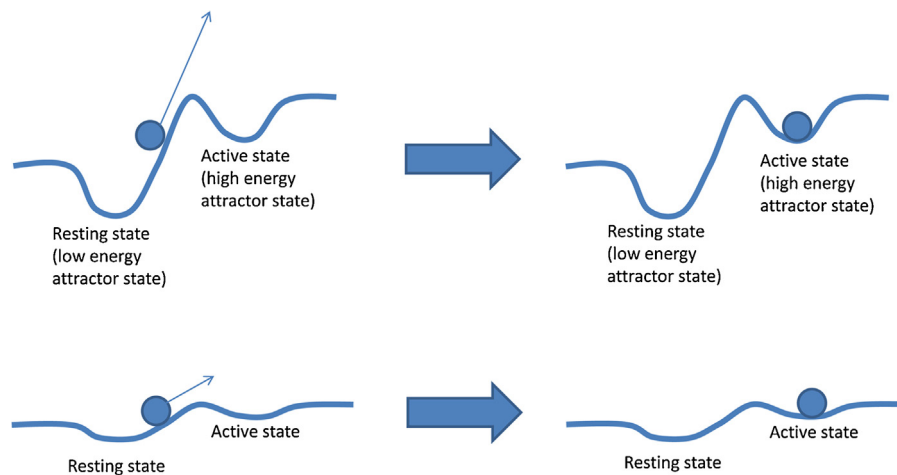


Fig. 3. State transitions in attractor networks, as visualized in an energy landscape. When at rest, each network is in a stable, low-energy state (e.g. a pingpong ball at the bottom of the valley, or a coin lying flat on the ground). When energy is applied to the network (i.e. dendritic stimulation occurs, or noise levels rise within the network itself), the network as a whole may enter another stable state at a higher energy level (e.g. a ping pong ball that has been moved uphill by some force and settles in a valley at the top, or a coin that is dropped onto the ground and starts to roll on its side). When the valleys in the energy landscape become shallower (lower two drawings, see main text for presumed mechanisms), differences in energy levels between active and resting states decrease, and only little energy (e.g. noise or dendritic stimulation) suffices for the network to make the transition from its resting state (e.g. true-negative perception) to its active state (i.e. false-positive perception or hallucination).

The shallowing of attractor basins can occur under various conditions. In healthy subjects, a well-known example is sensory deprivation. As demonstrated in numerous experiments during the 1950s through 1970s, the depatterning and deprivation of sensory information tends to evoke hallucinations in healthy participants within 24 h (Zubek, 1969). Such an extreme sensory disconnection from the external world corresponds with a lack of dendritic input and, hence, in a low-frequency firing rate of the attractor network and an increased likelihood of that network to roam the resting-state basins of the attractor landscape. Experientially, this is associated with weak perceptions of a fleeting nature since the lack of auto-excitation prevents the formation of strong and robust firing patterns (and, hence, the mediation of strong and robust percepts). Additionally, a lack of collateral inhibition (due to a lack of competing stimuli) decreases noise suppression and renders the network susceptible to any newly emerging stimuli. Individual neurons and neural networks at large have thresholds to prevent them from being accidentally activated, e.g. by low-intensity noise fluctuations. In the absence of high-energy stimuli, the neurons in the attractor network tend to lower their thresholds (e.g. to adapt to low stimulus intensities in a dark room). This process, known as neural adaptation (Clifford et al., 2007), leads to a shallowing of the attractor basins of the active as well as the resting state. Once this is achieved, even small amounts of energy will suffice to make the network switch from its low-energy resting state ('down in the valley') to a high-energy active state ('further uphill'). In the absence of any external stimuli, the energy needed for this 'uphill' trajectory in the energy landscape can be supplied by random depolarizations of the network itself (i.e., 'noise'), or by low-intensity dendritic input provided by any of the neighboring attractor networks that have crossed their thresholds of activation for similar reasons (Deco et al., 2011). As a consequence, robust percepts are formed in the absence of corresponding external stimuli. These robust percepts may induce the activation of other sensitized networks, thus producing a chain reaction of false-positive state transitions. When such state transitions occur in perceptual cortices, the individual experiences hallucinations. Similarly, when these events take place in higher-order cognitive brain regions, they evoke delusions.

5.2.2. Patients with psychosis

In psychotic patients, less extreme conditions than sensory deprivation suffice to produce hallucinations. Rolls et al. (2008)

explain this by linking the dynamics of attractor networks to deficiencies in gamma-aminobutyric-acid (GABA) and N-methyl-D-aspartate (NMDA) signaling found in patients diagnosed with schizophrenia (Sullivan and O'Donnell, 2012; Lisman et al., 2008; Benes and Gisabella, 2006; Coyle, 2006). Biochemically, the dynamics of attractor networks depends on specific neurochemical substances. Their positive feedback loops are created with the aid of NMDA-receptor activation by the excitatory neurotransmitter glutamate (Fig. 2). Reduced NMDA conductance reduces the robustness and firing rate of the active state, thus leading up to a shallowing of the attractor basins for this state (Loh et al., 2007). Collateral inhibition and noise reduction depend on GABA-receptor activation by the inhibitory neurotransmitter GABA (Klausberger and Somogyi, 2008). Therefore, GABA interneuron inefficacy will yield a decrease in the suppression of competing signals as well as a disinhibition of the resting state, both of which contribute to the shallowing of the attractor basin of the low-energy resting state. Thus, the resting and active state start to resemble each other in terms of energy levels, which facilitates transitions between the two states. As a consequence, a network with these characteristics will display loose and erratic jumps between low-frequency resting states and high-frequency active states (Loh et al., 2007; Durstewitz and Seamans, 2008). Experientially, these unanticipated state switches in human neocortex translate to the switching on and off of hallucinatory and delusional states.

Further support for the attractor network model comes from the elevated ratios of D2 versus D1-dopamine receptor activity found in prefrontal cortex in groups of patients diagnosed with schizophrenia (Braver et al., 1999). Throughout the human brain, basic excitatory and inhibitory signaling is modulated by neurotransmitters such as dopamine, (nor)adrenaline, serotonin, and acetylcholine. In attractor networks, these neurotransmitters shift the balance between NMDA-related and GABA-ergic signaling, thus producing shifts in signal-to-noise ratios (SNRs). Dopamine changes SNRs in favor of noise production by reducing GABA-ergic collateral inhibition, thus promoting the occurrence of hallucinations and delusions. Since chain reactions may occur in labile or sensitized attractor networks and only parts of these networks need to be triggered in order for it to engage in pattern completion, GABA-ergic and glutamatergic changes in patients diagnosed with schizophrenia may principally underlie loose associations. Clinically, this may manifest as 'jumping to conclusions', meaning that

patients show a tendency to link the occurrence of one event (e.g. their car breaking down) to another one (a visit from their mother) and, without much delay, assume that, for example, she must have been the one who sabotaged the car.

Similar to dopaminergic activity, noradrenergic stimulation (induced, for example, by stress) induces shifts in the SNR in favor of the false-positive detection of noise. The mechanism behind this involves a decrease in both GABA-ergic collateral inhibition and glutamatergic collateral excitation (Hasselmo et al., 1997). A possible reason for this is that stressful conditions require our perceptual and cognitive networks to be biased toward the false-positive detection of rivals, predators, and other threats. From the vantage point of evolution, this type of bias has important benefits for survival since it allows to minimize the false-negative detection of actual threats (e.g. not seeing a tiger when there is actually one there) at the cost of false-positive threats (i.e. hallucinations and delusions). In individuals whose attractor networks are already susceptible to false-positive states, these mechanisms increase the chance of experiencing hallucinations and delusions; this happens to many psychotic patients under stressful conditions.

Thematically, delusions and hallucinations can be valued positively or negatively by the person experiencing them and, in the general population, are indeed valued positively by a significant number of people (Daalman et al., 2011). However, in clinical populations many of those experiences involve situations of a threatening or otherwise frightening nature. This preference for negative stimuli again seems to involve a detection bias for rivals, predators, and other threats. In that sense, hallucinations and delusions can be regarded as an unfortunate price that is paid by some individuals for a critical survival mechanism (Dodgson and Gordon, 2009; Kelleher et al., 2010). Interindividual variation in this detection bias will cause some people to show an extreme sensitivity to such stimuli, especially under stressful conditions. Normally, alterations in dopaminergic and GABA-ergic functioning reach a climax in early adulthood (Uhlhaas, 2013). Together with the fact that stress levels (and hence noradrenergic activity) peak in early adolescence (Hatch and Dohrenwend, 2007), this may explain why the onset of psychosis-proneness tends to commence at this relatively early age.

5.3. Microstructural and genetic changes in psychosis

Apart from neurotransmitter concentrations, the dynamics of attractor networks at the microscale level of organization are also influenced by microstructural changes in the number and quality of synapses. It is suggested that the basis for psychosis-proneness is laid during the gestational period, even though the clinical signs of psychosis tend to become manifest no sooner than in late adolescence (Rapoport et al., 2012). It has been shown that the brains of healthy adolescents undergo massive pruning of (primarily) excitatory synapses (in conformity with the ‘use it or lose it’ principle) (Glantz et al., 2007; Gonzalez-Burgos et al., 2008). Due to this process, the loss of excitatory NMDA-ergic synapses tends to be more substantial in adolescents diagnosed with schizophrenia than in age-matched controls (Glantz and Lewis, 1999). The concomitant decrease in (auto)excitation of attractor networks might contribute to the instability of internal representations, and to the proneness of these individuals to hallucinations and delusions at a later age. Another factor that affects connectivity at the microscale level is the use of cannabis which, apart from the direct effects of its active compound tetrahydrocannabinol (THC) on neuronal signaling, affects the outgrowth of synaptic terminals (Harkany et al., 2008; Bossong and Niesink, 2010; Keimpema et al., 2011). The question why some individuals develop psychotic symptoms due to cannabis whereas others do not, is probably best answered with reference to inter-individual differences in synaptic density and expression levels of

the cannabinoid receptor. In individuals who have a local excess of synaptic connections, a tipping point may be reached under the influence of THC, thereby increasing the likelihood for psychotic symptoms to set in. Similarly, hallucinogens and other psychotogenic substances may alter neurotransmitter levels in attractor networks in favor of false-positive attractor states, and thus facilitate the mediation of positive symptoms of psychosis.

Another group of factors that may alter connectivity at the microscale level are immunocytochemical changes, which may interfere with neuronal signaling at the receptor level and with synapse formation at the microstructural level (The Network and Pathway Analysis Subgroup of the Psychiatric Genomics Consortium, 2015). This may tilt the balance of SNRs within attractor networks toward producing false-positive perceptions. A final factor that deserves to be mentioned in this context is histone methylation, the microbiological process that bridges the gap between environmental stress and levels of genetic expression (i.e. epigenetic changes). Extremely stressful events (e.g. psychotrauma) may cause particular genes to switch on or off through histone methylation, leading to more or less permanent changes in gene expression profiles (e.g. profiles compatible with an enhanced alertness to stressful stimuli). In accordance with the hostile environment in which such changes take place, acquired changes in genetic expression levels shift SNRs in attractor networks in favor of the early detection of such threats; again, the experience of positive symptoms is the price that is paid for an increased ability to pick up true-positive threats (Dodgson and Gordon, 2009; Kelleher et al., 2010).

5.4. Clinical lessons from the microscale level

The number one evidence-based treatment option for psychotic symptoms at the microscale level is the administration of D2 antagonists (i.e. ‘antipsychotics’). In psychotic patients these substances increase GABA-ergic currents (Seamans and Yang, 2004), thus correcting GABA-ergic deficiencies and suppressing noise levels in networks surrounding the attractor network. As a result, attractor networks become more resistant against switches from low-energy (true-negative) resting states to high-energy (false-positive) persistent states. In theory, the administration of D1-receptor agonists (e.g. psychostimulants such as methylphenidate) should be able to produce deeper attractor basins of the persistent state, since these substances increase NMDA-mediated auto-feedback within attractor networks (Rolls et al., 2008). This prevents the occurrence of state switches from high-energy to lower-energy attractor states and helps produce more robust percepts, which is the basic aim of psychostimulant treatment in patients diagnosed with attention-deficit (hyperactivity) disorder (AD(H)D). This hypothesis also explains why methylphenidate monotherapy should not be prescribed for AD(H)D patients with comorbid positive symptoms of psychosis, since this might lead to default stabilization of their hallucinations and delusions. Since beta-adrenergic stimulation decreases GABA-ergic noise suppression and facilitates the formation of false percepts in already vulnerable attractor networks, psychotic symptoms may also be reduced by prescribing either direct GABA-ergic agonists (i.e., benzodiazepines) or beta-adrenergic antagonists (beta blockers).

To summarize, a simple model of excitation, inhibition, and modulation within interconnected attractor networks allows to explain various psychotic phenomena, to provide a rationale for conventional anti-psychotic interventions, and to facilitate the exploration of novel interventions. The agents in this model are brought off balance by an array of different processes, globally involving neurochemical, neuroinflammatory, microstructural, and (epi)genetic alterations, whereas therapeutic interventions target these global pathogenetic pathways by shifting SNRs within

the attractor networks back from false-positive to true-negative values.

In the following sections, we connect this state of affairs at the microscale level of organization with those occurring at higher-scale levels of organization.

6. Network models of psychosis: the mesoscale level

6.1. Structural and functional connectivity

Until about a decade ago, voxel-based morphometry (VBM) of structural MRI data was among the most popular *in vivo* neuroimaging techniques used to localize brain areas in which gray-matter volume (GMV) correlated with some variable of interest (e.g. task performance or positive symptom scores). Similarly, diffusion tensor imaging (DTI) was used to relate local differences in white-matter tract integrity to certain variables of interest (Basser and Pierpaoli, 1996). Most functional MRI studies involved the localization of discrete brain areas in which activity markers such as the Blood Oxygenation-Level Dependent (BOLD) response correlated with phenotypical markers. During the past decade, this non-relational approach gradually made place for a relational (network-based) approach. This development was largely made possible by methodological advances and the discovery of small-world networks (outlined above). From the perspective of network science, 'alterations in GMV' can be regarded as 'changes in network nodes', whereas 'local changes in white-matter-tract integrity' can be regarded as 'changes in network links'. Brain connectivity studies traditionally distinguish between two types of connectivity, i.e., structural, and functional connectivity (Bullmore and Sporns, 2009). Structural connectivity can metaphorically be compared to the actual glass-fiber cables that allow for information exchange across the World Wide Web, whereas functional connectivity is comparable with the links between .html pages on the Internet. Such pages may link directly to each other, even though several servers and routers can be involved in connecting the actual computers on which the pages are stored. Thus, structural-connectivity studies focus on the actual white-matter tracts that run between different areas of gray matter, whereas functional imaging techniques such as fMRI, EEG, and MEG are used to study statistical associations between the neurophysiological states of gray-matter regions that may be located various structural degrees of separation apart from each other. Since network studies examine relationships between brain areas rather than individual brain areas themselves, current neuroimaging studies allow to explore structural and functional correlates of positive symptoms at an unprecedented level of integration.

Previous studies show that both structural and functional connectivity maps are characterized by a small-world and scale-free topology (Bullmore and Sporns, 2009). As a consequence, the human brain at the mesoscale level of organization seems to display the same general network architecture as the attractor networks rendered in Fig. 1. However, a major difference is that, in this case, the neurons in Fig. 1 do not represent single cells but rather substantial clusters of gray matter. The structural connections between these clusters of gray matter are not formed by single axons, but by white-matter fiber tracts that can be visualized *in vivo* with the aid of neuroimaging techniques. Functional connections, on the other hand, consist of statistical relationships between activity levels in these areas. In comparison with neural networks at the microscale level of organization, connectivity maps at the mesoscale level of organization involve highly integrated and multimodal brain states that correspond to full-blown mental representations. Sensory cortices provide integrated representations of the organism's *milieu externe*, medial temporal and limbic

structures integrate information from the sensory domains with emotional and cognitive information, medial prefrontal (anterior cingulate) and (dorsal) anterior insular regions have a function in salience detection regarding this data stream, striatal structures are involved in developing motivational drive and initiating automatic response patterns, and dorsolateral prefrontal areas are involved in effortful response selection and conscious executive functioning, while the actual planning and execution of motor output takes place in prefrontal (premotor) and motor cortices (Sridharan et al., 2008). Together, these processes are referred to as 'cognitive control'. Three canonical networks can be distinguished within the set of brain regions involved (Sridharan et al., 2008): the *central executive network* (CEN) is predominantly active during the execution of goal-directed task performances, and relies on dorsolateral prefrontal and posterior parietal areas. As soon as individuals cease to perform in a goal-directed manner and engage in a state of quiet wakefulness (i.e., with eyes closed, but awake), activity levels within the CEN drop to a minimum whereas activity levels in a set of brain regions comprising the *default-mode network* (DMN) show a simultaneous increase. The DMN comprises medial prefrontal regions, posterior cingulate, dorsal parietal regions, and mediotemporal regions. Activity within these regions is associated with mind-wandering, fantasizing, musing, autobiographical recollection, daydreaming, and actual dreaming (Deco et al., 2011). Finally, anterior cingulate and (dorsal) anterior insular regions are part of a so called *salience network* (SN), which has a key role in salience detection and in switching between goal-directed CEN activity and reflective DMN activity. The CEN, DMN, and SN appear to be of crucial importance in the pathogenesis of positive symptoms (Manoliu et al., 2014). Below, we discuss the current neuroimaging literature on psychosis from the perspective of structural and functional connectivity studies involving these networks, whereas the results of VBM and DTI studies are discussed only in relation to changes in network nodes and links as reported in connectivity studies.

6.2. Structural connectivity and psychosis

Whole-brain structural connectivity maps of patients diagnosed with schizophrenia show a reduction of values of small-worldness parameters. Some examples include the loss of frontotemporal and insular hubs, the emergence of novel non-frontal hubs (Bassett et al., 2008; Van Den Heuvel and Sporns, 2011), a lowering of the clustering coefficient (Fornito et al., 2012; Alexander-Bloch et al., 2010), the randomization of connectivity (Lynall et al., 2010; Bassett et al., 2008), increases of path lengths, and the reduction of interregional connectivity (Pettersson-Yeo et al., 2011). The loss of frontotemporal and insular hubs may correspond with previous VBM findings involving the loss of GMV in medial prefrontal, (superior) temporal, insular, thalamic, striatal, and cerebellar regions (Shepherd et al., 2012; Fusar-Poli et al., 2012; Fornito et al., 2009; Allen and Modinos, 2012; Gaser et al., 2004; Neckelmann et al., 2006; Martí-Bonmatí et al., 2007; Nenadic et al., 2010). Similarly, the emergence of novel hubs may correspond with previous findings of an increased GMV in areas associated with delusion-proneness (Sigmundsson et al., 2001; Wang et al., 2012; Whitford et al., 2009). An increase in the randomness of wiring patterns may explain the inconsistency of previous DTI findings in patients diagnosed with schizophrenia, varying from a global decrease in white-matter-tract integrity associated with 'schizophrenia' (Sommer et al., 2012) to decreases specifically associated with verbal auditory hallucinations, in the white-matter-tract integrity of medial prefrontal areas (Van Tol et al., 2013; Rotarska-Jagiela et al., 2009, 2010), medial temporal areas (Ellison-Wright and Bullmore, 2009), and the superior and inferior longitudinal fasciculus (Seok et al., 2007; Shergill et al., 2007; Hubl et al., 2004; Szeszko et al., 2008; Chan et al., 2010). Most of these findings involve the loss of

prefrontal connections, which corresponds with the loss of important hub regions in the same areas found in patients diagnosed with schizophrenia.

Generally speaking, a loss of small-world topology is associated with a decrease in the quality and efficiency of information processing which is, in turn, experienced as a slowing-down of cognitive abilities and processing speed. Regarding alterations in specific brain regions, a loss of frontal hubs seems to be associated with a reduced capacity for integration, abstraction, and creation of overview (Van Den Heuvel and Sporns, 2011). Reduced integration is thought to result in the loosening of cognitive associations, a symptom historically marked as a core feature of schizophrenia (Bleuler, 1908; Friston and Frith, 1995). The central role of the anterior cingulate and (anterior) dorsal insular region in salience detection has sparked the hypothesis that decreased GMVs within these frontal areas may lead patients to attribute enhanced salience to sensory events and erroneously attribute endogenously mediated percepts to external sources (Jardri et al., 2013; Allen et al., 2008; Fletcher and Frith, 2010). The dissolution of higher-order (prefrontal) clusters may reduce collateral inhibition by competing attractor states, thus leading to a disinhibition of lower-level clusters and, ultimately, the mediation of hallucinations and/or delusions (Bassett et al., 2008). In addition, a loss of hubs may interfere with the ability to discriminate between stimuli and concepts (Zalesky et al., 2011). Such changes may also promote the aforementioned 'jumping to conclusions', whereas increased randomness of anatomical connections – possibly the result of the excessive pruning of synapses (Hoffman and McGlashan, 2001) may promote bizarre delusions and hallucinations.

Finally, the network structure of psychotic symptoms at the phenotypical level indicates that hallucinations may simply trigger delusional explanations of these percepts (a bottom-up genesis of delusional activity). There is also evidence for the reversed causal direction, i.e., delusions triggering hallucinations in a top-down manner. In the latter case, higher-order conceptual regions may enhance selective attention (i.e. alertness) to particular stimuli, such as facial expressions or policemen in the street. Such top-down effects involve increased dopaminergic and adrenergic signaling within primary sensory cortices (Dodgson and Gordon, 2009; Kelleher et al., 2010; Markovic et al., 2014), which may shift SNRs in favor of false-positive attractor states.

6.3. Functional connectivity and psychosis

Changes in functional connectivity maps in psychotic disorders resemble those in structural connectivity maps to a considerable degree (Goekoop and Looijestijn, 2012). Again, a loss of small-worldness parameters can be observed in terms of increased randomness of (frontal) connectivity patterns (Cole et al., 2011) and a loss of frontal hubs. Since functional connectivity is thought to lie closer (process-wise) to phenotypical experience, the study of functional connectivity may yield important information on the origins of the psychotic phenotype. Functional connectivity studies typically examine associations between scores on phenotypical markers and connectivity maps calculated across various different brain states that globally involve central executive, salience-related, and default-mode states. As observed above, these global networks are differentially activated during wakeful and sleeping states of the human brain (with a preference for DMN activity during dreaming and CEN during active task performance). Since positive symptoms by definition occur during wakefulness, we limit our discussion of mesoscopic changes in psychosis to functional connectivity maps during the wakeful state.

Due to the scale-free nature of the network that constitutes the human brain, similar rules apply at different scale levels of organization. Starting from that general principle, the CEN and

the DMN are conceptualized as giant attractor networks at the mesoscopic level of organization that are in a constant state of mutual competition. The CEN is engaged in auto-excitation during task performance, while suppressing the activity of the DMN through collateral inhibition. The reverse happens when the individual enters a state of quiet wakefulness (not to be confused with the 'resting state' of microscale-level attractor networks), and the DMN in turn gears up from its low-energy resting state to a high-energy active state. In this state, the DMN engages in auto-excitation and in collateral inhibition of the CEN. Crucially, the salience network (dorsal anterior insula and anterior cingulate cortex) is responsible for biasing the competition between DMN and CEN activity levels (Sridharan et al., 2008). In psychotic disorders, both auto-excitation and collateral inhibition are impaired. Comparable to what happens at the microscale level of organization, this leads to the formation of instable percepts during active states and to insufficient suppression of noise in competing (resting state) networks. At the mesoscopic level of organization, this combination of an increase of noise levels and a decrease of the resistance against intrusion by noise, facilitates the mediation of false percepts. Therefore, on the one hand, positive symptoms may be due to insufficient suppression of (noise generated by) the DMN during task performance. Additionally, a decrease in auto-excitation of the CEN will render this network more susceptible to noise intrusions from the DMN. Once DMN activity 'overrules' the already labile CEN, it becomes manifest at the experiential level in the form of clear, consciously experienced delusions and/or hallucinations of a multimodal, integrated, and complex nature. In this sense, psychosis is comparable to a state of 'dreaming-while-awake', or a blending of endogenously and exogenously mediated representations. On the other hand, the activity of the DMN is also labile (Northoff and Qin, 2011) and, therefore, susceptible to intrusions by insufficiently suppressed noise generated by the CEN. Experientially, such CEN intrusions into the DMN may produce a phenotype where actual events are experienced as unreal or dreamlike, as in derealization or depersonalization. Moreover, noise generated by the CEN that overrules the DMN may provide the neurophysiological correlate of delusions of control.

In summary, insufficient noise suppression and increased susceptibility to noise intrusions within both the CEN and the DMN network may promote the blending of information processing between these two anticorrelated networks and mediate specific positive symptoms of psychosis. We will first discuss evidence for the hypothesis that network states spill over from the DMN to the CEN. After that, we will discuss the evidence for psychotogenic mechanisms in the opposite direction.

Various observations seem to confirm the hypothesis that an excess of DMN noise is responsible for the emergence of positive symptoms. For instance, insufficient suppression of DMN activity during task performance is a common finding in patients diagnosed with schizophrenia (Garrity et al., 2007; Meyer-Lindenberg et al., 2005; Jeong and Kubicki, 2010; Woodward et al., 2011). This indicates that these patients may be more susceptible to noise intrusions originating from the DMN, experienced by them in the form of hallucinations and/or delusions (Northoff and Qin, 2011). Additionally, administration of ketamine (a NMDA receptor antagonist) induces hyperconnectivity within (i.e. increases the robustness of activity within) the DMN, which is associated with the severity of positive symptoms induced by this substance (Driesen et al., 2013). DMN hyperactivity is most likely due to a net decrease in GABA-ergic signaling. This decrease may involve an isolated neurochemical deficiency, or a structural loss of fronto-temporal (inhibitory) hubs observed in schizophrenia. Indeed hypoconnectivity of (inhibitory) anterior cingulate and (dorsal) anterior temporal regions is specifically related to hyperconnectivity within auditory cortex in general (Rotarska-Jagiela et al., 2010) and the

occurrence of verbal auditory hallucinations in particular (Mechelli et al., 2007; Vercammen et al., 2010). Reduced input from speech perception areas, such as Wernicke's, to frontal areas such as Broca's, as established with measures of effective connectivity in hallucinating patients (Curcio-Blake et al., 2013), may be analogous (at the mesoscale level of organization) to the sensory-deprivation effect described earlier in this paper. The loss of frontal (inhibitory) hubs in schizophrenia to a large degree involves the salience network, which is responsible for biasing the balance between DMN and CEN activity levels. The salience network (SN) can therefore be conceived as the meso-scale equivalent of the GABA-ergic interneurons shown in Fig. 2, which has a modulatory influence on both attractor networks (CEN and DMN). Thus, a loss of frontal hubs may impair GABA-ergic noise suppression of the DMN, which 'jams' the CEN with noise that is experienced actively and consciously in the form of hallucinations or delusions. The role of the predominantly dopaminergic salience system in appraising and balancing DMN and CEN activity is in line with the dopamine hypothesis for the mediation of psychotic symptoms (Palaniyappan and Liddle, 2012). A disconnection between prefrontal cortex and hippocampus during (working-memory) task performance has been linked to the severity of positive symptoms (Henseler et al., 2010). In the latter situation, hippocampal activity is insufficiently suppressed. Such findings have given rise to the memory hypothesis of hallucinations, which states that hallucinations at least partly represent insufficiently suppressed memories (Sommer et al., 2012). Since hippocampal regions are part of the DMN, the memory hypothesis fits the global picture of insufficient noise-reduction in DMN areas as a precondition for the occurrence of positive symptoms. Moreover, various studies have shown that losses of prefrontal function are associated with increased activity within auditory areas of the temporal lobe and the experience of verbal auditory hallucinations (e.g. Allen et al., 2008). Since these regions are part of the CEN, such findings fit the notion that aberrant DMN activity eventually overrules the CEN, resulting in the active and conscious perception of hallucinations.

All the findings discussed so far are in line with the notion of insufficient collateral inhibition of the DMN by the salience network and CEN, as well as with the notion of increased susceptibility of the CEN to noise intrusions due to a lack of auto-excitation and the resulting instability of its neural activity patterns. However, as indicated, the reverse causal direction is also possible, i.e. positive symptoms of psychosis being due to a disinhibited CEN and instability of DMN activity patterns, possibly mediated by a dysfunctional salience network. Various empirical observations support this mechanism. Jardri et al. (2013) studied the spatial and temporal stability of the DMN and association sensory cortices during hallucinatory episodes, and found that instability of the DMN correlates positively with the severity of hallucinations. Similarly, increases in DMN variability have been described by Garrity et al. (2007), while a loss of local connectivity within anterior and posterior cingulate subclusters of the DMN correlates with positive symptom scores (Skudlarski et al., 2010; Rotarska-Jagiela et al., 2010) report reduced connectivity (i.e. instability) in right inferior parietal cortex and the left hippocampus in association with hallucinations and delusions. Thus, disinhibition of the CEN also seems capable of mediating positive symptoms of psychosis. So far, however, most studies show hyperconnectivity as well as reductions of path length in the DMN (Becerril et al., 2011; Fornito et al., 2011; Wang et al., 2011), which suggests that the instability of the DMN is less pronounced than that of the CEN. As a corollary, positive symptoms of psychosis may be primarily associated with DMN noise affecting the CEN (a bias that may be the result of impaired functioning of the salience network), which is in conformity with the *dreaming-while-awake* hypothesis. However, other networks may also be relevant, such as the salience network and the amygdala

(Blanc et al., 2014; Escartí et al., 2010), which deserve more detailed examination in future studies.

In conclusion, the mechanisms that govern the mediation of psychotic symptoms at the mesoscale level of organization seem to resemble those at work at the microscale level of organization. Moreover, at all levels of organization, positive symptoms of psychosis would seem attributable to disorders of salience (Van Os, 2009) since eventually they involve non-adaptive changes in signal-to-noise ratios in favor of the conscious perception of noise. Although this hypothesis is in line with the scale-free nature of the human brain as predicted by network science, further empirical studies are needed to test its validity.

6.4. Clinical lessons from the meso level

The attractor network model at the meso level explains why patients often report that hallucinations and delusions decrease when they listen to music, sing, hum, whistle, go for a hike, or talk to others. Activities such as these induce strong active states in the CEN that compete with false-positive active states in the DMN through the process of collateral inhibition. This is an important biological reason why patients should be encouraged to seek a stimulus-rich environment, engage in social and physical exercise, or conduct any other kind of activity that requires executive action. Indeed, cognitive behavioral therapy (CBT) can be seen as a systematic effort in gaining active, verbal, conscious cognitive control over overly intrusive DMN states. The re-evaluation of what is salient and what is not is a crucial aspect of this therapy, since it aims to alter activity in the SN and promote a better balance between CEN and DMN states. So far, behavioral activation and CBT seem to be the most effective interventions that are aimed at the meso level. Evidence that physical stimulation methods such as transcranial magnetic stimulation, transcranial direct current stimulation and electroconvulsive therapy are effective against psychotic symptoms is currently weak (Nieuwdorp et al., 2015).

7. Network models of psychosis: the macroscale level

The macroscale level of organization takes us beyond the realm of the human brain with its micro- and mesoscale levels, into the world of social networks. As noted above, the same mathematical principles that govern the latter levels of organization are applicable here (Christakis and Fowler, 2009). Thus, social networks can be analyzed using the same algorithms used to calculate cerebral network clusters and network metrics. Previous studies have shown that social networks form communities in which individuals try to be as similar as possible (referred to as 'copy-cat' behavior, homophily, or *mimesis*) (Christakis and Fowler, 2009). Subjects at the center of such social communities tend to be healthier, happier, and more at ease than those residing at the periphery (Fowler and Christakis, 2008; Cacioppo et al., 2009). Comparable to the way attractor networks promote their own activity at the cost of those surrounding them, social clusters are in a constant state of mutual competition. At the macroscale level of organization that may translate to a constant desire of individuals to blend into their own community (the 'in-group') and affirm their common norms and values, whereas individuals living at the borders of the cluster are constantly tested for conformity or otherwise pushed toward another cluster (the 'out-group'), when considered 'different'. As a result, these people are more often exposed to feelings of rejection, social tensions, and habitual paranoia (Cacioppo et al., 2009). In the field of psychosis research, this mechanism has been substantiated by the work of Veling et al. (2014), who found that the risk for psychotic symptoms tends to decrease as a function of ethnic density. Ethnic density is a measure for the proportion of

inhabitants who are members of the patient's own ethnic group, and Veling et al. (2008) found that living in a neighborhood with a higher ethnic density is associated with a lower chance to develop psychotic symptoms. In network terms, being part of a community of individuals with a similar ethnic background (an 'in-group') apparently protects against psychosis, whereas the risk for psychosis increases outside such a neighborhood cluster. Since social isolation and rejection rank among the most stressful events, the latter situation increases the likelihood of actual paranoia and psychosis through the process of a stress-induced false-positive identification of threats (false alarms) as described above. Additionally, social deprivation can lead to psychosis in a way that is analogous to sensory deprivation as described in the section on the brain's microscale level of organization. According to the social-defeat hypothesis by Selten et al. (2013), prolonged social exclusion promotes enhanced baseline activity and/or sensitization of the dopamine system, thus increasing the risk for psychosis. Indeed, evidence for increased dopamine release in the striata of young people with hearing impairment, who may be at increased risk for psychosis, has recently been reported (Gevonden et al., 2014). Thus, the macroscale level can be linked to the mesoscale level through studies of social neuroscience in schizophrenia (Krabbendam et al., 2014). Stigmatization and social exclusion can create a vicious circle, with social isolation promoting psychotic symptoms and psychotic behavior promoting social exclusion, etcetera. This circle is bound to be more active in people already at risk for developing psychotic symptoms (Kirkbride et al., 2014). Therefore, in addition to the micro- and meso-scale levels that are habitually targeted with the aid of antipsychotic medication and CBT, antipsychotic interventions should also target the macroscale community level. Just as community medicine enforces adequate sanitation and hygienic measures at a community level, community psychiatry should focus on psychohygienic measures at the level of families, neighborhoods, villages, cities, states, and countries.

8. Conclusion

The Integrated Network Model of Psychotic Symptoms (INMOPS) allows to describe the positive symptoms of psychosis and their neurobiological correlates at three (subsequent) scale levels of organization (Fig. 1). At the microscale and mesoscale levels of organization, it allows for the description of individual psychotic symptoms and their relation with each other, together with descriptions of their mediation by structural and functional alterations in attractor networks. Empirical evidence for the validity of the mechanisms examined is provided by studies describing changes in neurotransmitter signaling pathways, in synaptic density and function, and in (environmentally-induced) genetic expression profiles, as well as by studies of structural and functional neuroimaging. At the macroscale level of organization, the model allows for the description of social mechanisms that influence the risk for psychosis. Starting from the premise that each of these scale levels of organization is governed by small-worldness, and that the network as a whole ('from molecule to mind') is essentially scale-free in nature, the model allows for the application of the same mathematical framework and corresponding language at each of its levels of organization. This allows to indicate at each scale level, and across scale levels, how alterations in network structure and function increase or decrease the likelihood for psychotic symptoms to occur. Rather than attempting to 'solve the schizophrenia problem' by proposing a hypothetical lathomenology to explain the connection between its multiple symptoms and multiple risk factors, the INMOPS attempts to explain the likelihood for various positive symptoms of psychosis to co-occur with reference to the principle of self-organization. Despite the considerable heterogeneity of

factors considered characteristic of 'schizophrenia', this opens up a new avenue toward a unified framework for understanding this complex group of symptoms and their mediation.

Acknowledgements

We would like to acknowledge Parnassia Psychiatric Hospital for granting research time to the first (JL), second (JDB) and last authors (RG).

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